The effect of nimodipine on cerebral oxygenation in patients with poor-grade subarachnoid hemorrhage

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Object. Nimodipine has been shown to improve neurological outcome after subarachnoid hemorrhage (SAH); the mechanism of this improvement, however, is uncertain. In addition, adverse systemic effects such as hypotension have been described. The authors investigated the effect of nimodipine on brain tissue PO2.

Methods. Patients in whom Hunt and Hess Grade IV or V SAH had occurred who underwent aneurysm occlusion and had stable blood pressure were prospectively evaluated using continuous brain tissue PO2 monitoring. Nimodipine (60 mg) was delivered through a nasogastric or Dobbhoff tube every 4 hours. Data were obtained from 11 patients and measurements of brain tissue PO2, intracranial pressure (ICP), mean arterial blood pressure (MABP), and cerebral perfusion pressure (CPP) were recorded every 15 minutes.

Nimodipine resulted in a significant reduction in brain tissue PO2 in seven (64%) of 11 patients. The baseline PO2 before nimodipine administration was 38.4 ± 10.9 mm Hg. The baseline MABP and CPP were 90 ± 20 and 84 ± 19 mm Hg, respectively. The greatest reduction in brain tissue PO2 occurred 15 minutes after administration, when the mean pressure was 26.9 ± 7.7 mm Hg (p < 0.05). The PO2 remained suppressed at 30 minutes (27.5 ± 7.7 mm Hg [p < 0.05]) and at 60 minutes (29.7 ± 11.1 mm Hg [p < 0.05]) after nimodipine administration but returned to baseline levels 2 hours later. In the seven patients in whom brain tissue PO2 decreased, other physiological variables such as arterial saturation, end-tidal CO2, heart rate, MABP, ICP, and CPP did not demonstrate any association with the nimodipine-induced reduction in PO2. In four patients PO2 remained stable and none of these patients had a significant increase in brain tissue PO2.

Conclusions. Although nimodipine use is associated with improved outcome following SAH, in some patients it can temporarily reduce brain tissue PO2.

KEY WORDS • subarachnoid hemorrhage • cerebral oxygenation • nimodipine

Several randomized clinical trials and a metaanalysis of these trials have demonstrated that the prophylactic administration of nimodipine, a dihydropyridine calcium antagonist, is associated with improved outcome following aneurysmal SAH.1,12,34,39-41 These trials were undertaken with the expectation that nimodipine, which has a relative specificity for the cerebral vasculature,26,29,96 would ameliorate the poor outcome associated with vasospasm. Furthermore, because nimodipine blocks dihydropyridine-sensitive (L-type) channels found in the smooth-muscle cells of major cerebral arteries and arterioles, it was postulated that nimodipine would reduce vasospasm. The various clinical trials and other clinical series, however, demonstrated angiographically that vessel caliber was not influenced by nimodipine and that the incidence of symptomatic vasospasm was not associated with nimodipine use.1,3,12,13,39-41

The exact mechanism by which nimodipine improves outcome after SAH remains unknown. Its clinical effects have been attributed to the blockade of calcium-dependent excitotoxicity,42,47 antplatelet aggregation,21 dilation of leptomeningeal arteries or small collateral vessels not seen on angiograms,2 and inhibition of red blood cell product--induced ischemia.46 Nimodipine use, however, is also known to have several adverse effects. For example, nimodipine can induce hypotension and lead to significant hemodynamic alterations in patients.43,44,53 In addition, treatment with nimodipine can lead to variable changes in CBF, with some studies demonstrating a nimodipine-induced increase in CBF and others failing to demonstrate this effect.54-55,41,42 Similarly, in an experimental model of SAH nimodipine led to a brief initial decrease in CBF.49 Not long ago, the administration of nimodipine for traumatic SAH was described as a rare cause of systemic hypoxemia4 and was associated with significant changes in fibrinolytic activity.46 Thus, the relationship between calcium-channel blocking agents, vasospasm, CBF or adequacy of CBF, and SAH is complex and not fully understood.

Recently, it has become possible to measure brain tissue PO2 and other aspects of cerebral metabolism. This monitoring of cerebral metabolism and brain tissue PO2 is safe and can be useful in neurosurgical critical care.45,47,28,7,26,9,11 We therefore undertook this study to examine the effects of ni-
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Nimodipine on brain tissue PO2. Our results demonstrate that some patients receiving standard nimodipine treatment experience a time-dependent but transient reduction in brain tissue PO2, immediately after treatment. This reduction in pressure is independent of changes in CPP.

Clinical Material and Methods

Patient Population

Patients with aneurysmal SAH admitted to the Hospital of the University of Pennsylvania, a Level I trauma center, during a 6-month period were considered for this study. Inclusion criteria for the study were the following: 1) poor clinical grade following an SAH (Hunt and Hess Grade IV or V); 2) no evidence of cardiac failure; 3) brain tissue PO2, monitoring; 4) nimodipine administration; and 5) stable blood pressure. Each patient had undergone volume resuscitation and had been stabilized for at least 12 hours before the observation period. Patients were evaluated as part of a prospective observational database that had been given Institutional Review Board approval.

Case Management

Patients were treated according to a standard policy that included the following: 1) aggressive prehospital and preoperative resuscitation; 2) admission to the neurosurgical ICU; 3) intubation and mechanical ventilation; 4) early aneurysm occlusion achieved using surgical or endovascular techniques based on the structure of the aneurysm; 5) removal of surgical mass lesions; and 6) prevention and treatment of secondary cerebral injuries.31 While the patients were in the neurosurgical ICU, they received ICP, brain tissue PO2, and invasive hemodynamic monitoring. External ventricular drains were inserted in patients with hydrocephalus or intraventricular hemorrhage. Ventilator management was tailored to maintain a PaO2 level greater than 100 mm Hg and a PaCO2 level between 30 and 35 mm Hg. All patients received baseline crystalloid infusions of 0.9% normal saline and 20 mEq/L of KCl at a rate of 100 ml/hour, starting at the time of admission and continuing until post-SAH Day 14. Central venous pressure was measured hourly and maintained between 5 and 10 mm Hg by providing albumin and crystalloid boluses. Patients were given transfusions of packed red blood cells if their hematocrit levels were less than 30%. Daily TCD measurements were performed. In patients demonstrating moderate or severe vasospasm, hypervolemia was induced. If these patients became symptomatic, hypertension was induced by administering phenylephrine; if they continued to have symptoms from vasospasm, balloon or papaverine angioplasty was performed. Anticonvulsant medication (Dilantin) was administered for 2 weeks or longer if seizures occurred. Nimodipine (60 mg) was administered through a nasogastric or Dobhoff tube every 4 hours. The MAPB was closely monitored; patients who required neosynephrine to maintain their blood pressure or whose MABP was reduced by the nimodipine were excluded from this study.

Physiological Measurements and Brain Tissue PO2 Monitoring

The following parameters were continuously monitored:

1) heart rate by using a 12-lead electrocardiography unit; 2) MABP with the aid of a radial artery catheter; 3) SaO2 by means of pulse oximetry; 4) end-tidal CO2; 5) ICP by using an intraparenchymal ICP monitor (Camino; Integra NeuroSciences, Plainsboro, NJ) or ventricular catheter; 6) brain temperature by using an intraparenchymal temperature probe (Licox; Integra NeuroSciences); and 7) local brain tissue PO2 with the aid of an intraparenchymal Clark-type electrode (Licox; Integra NeuroSciences). Cerebral perfusion pressure was calculated from the measured parameters (CPP = MABP − ICP). Monitoring probes specific to ICP and brain tissue temperature and PO2 were inserted into the frontal white matter of the patient and provided continuous on-line measurements of these physiological variables.

Data Collection and Statistical Analysis

Values of the physiological variables were continuously recorded (Component Monitoring System model M1046-9090C; Hewlett-Packard, Andover, MA) and noted every 15 minutes on the ICU flow sheet. Cerebral perfusion pressure, MABP, and brain tissue PO2 were analyzed before administration of nimodipine and at 15-minute intervals after the drug was given, with each patient serving as his or her internal control. The results of univariate analysis are summarized as means ± SDs or as medians and ranges if samples departed substantially from normal distributions. Differences between the values of variables before and after nimodipine administration were evaluated using the Student t-test, and linear relationships were examined using Spearman correlations. Significance was assigned a probability value lower than 0.05. All univariate and bivariate analyses were performed using a commercially available software package (SAS version 8.2; SAS Institute, Inc., Cary, NC).

Results

Patient Characteristics

Twenty-four patients with poor-grade SAH (Hunt and Hess Grade IV or V) following aneurysmal SAH were admitted to the Hospital of the University of Pennsylvania during a 6-month period. There were five men and 19 women and the median patient age was 59.6 years (range 25.7–78.6 years). Thirteen of these patients were excluded from this study because they experienced a nimodipine-associated reduction in MABP or were hemodynamically unstable, despite treatment with vasopressors and fluid resuscitation (nine patients), or because they did not undergo brain tissue PO2 monitoring (four patients). Eleven patients, three men and eight women (mean age 64.3 ± 10.9 years), are described in this report. The clinical characteristics of the various patients are listed in Table 1.

Nimodipine and Brain Tissue PO2

All observations were recorded within 7 days of the SAH. Seven (64%) of 11 patients demonstrated transient reductions in brain tissue PO2 following nimodipine administration (Table 1). The mean baseline O2 pressure value measured in these seven patients was 38.4 ± 10.9 mm Hg (Fig. 1). Twenty-six instances of nimodipine administration were...
Physiological Variables

In the 11 patients in this study, including the seven patients in whom brain tissue PO₂ decreased, the fraction of inspired O₂, SaO₂, end-tidal CO₂, heart rate, and ICP remained stable during nimodipine administration. The baseline measurements of MABP and CPP were 90 ± 20 and 84 ± 19 mm Hg, respectively (Figs. 2 and 3). In these patients the MABP and CPP were not significantly different from baseline values 15 minutes after nimodipine was administered (MABP 79 ± 27 mm Hg; CPP 80 ± 11 mm Hg) or at a later time. Although there were fluctuations in ICP, recorded in these seven patients. The greatest reduction in brain tissue PO₂ occurred within 15 minutes of nimodipine administration, when the pressure was reduced to 26.9 ± 7.7 mm Hg (p < 0.05). Cerebral oxygenation remained significantly reduced for 60 minutes after nimodipine administration and measured 27.5 ± 7.7 mm Hg and 29.7 ± 11.1 mm Hg at 30 and 60 minutes, respectively (p < 0.05 for both measurements). Brain tissue PO₂, returned to baseline values within 2 hours of nimodipine administration (35.2 ± 9.5 mm Hg). In the remaining four patients (36%) the PO₂ remained stable and a significant increase was not observed in any of these patients.

Transcranial Doppler Findings

All patients underwent TCD ultrasonography daily. In those patients in whom there was a transient reduction in brain tissue PO₂, no evidence of moderate or severe vasospasm was observed on TCD studies obtained on the same day and within 3 hours of the reduction in brain tissue PO₂. Among patients in whom a nimodipine-induced reduction in PO₂ occurred, bilateral MCA and anterior cerebral artery blood flow velocities were consistently less than 120 cm/second and no significant changes (> 50 cm/second) were found during serial examinations. Similarly, significantly elevated or large changes in blood flow velocities were not observed on serial TCD examinations in the four patients in whom brain tissue PO₂ was stable.

Clinical Variables

To determine if there were any predictive factors for a nimodipine-induced reduction in brain tissue PO₂, we examined the variables listed in Table 1. The premorbid clinical and radiographic variables were similar in patients who did and those who did not experience a nimodipine-induced reduction in brain tissue PO₂. Patients whose brain tissue PO₂ was stable on average weighed more than those whose pressure decreased (p < 0.05) and tended to have a slightly higher ICP. They also were less likely to have a preexisting cardiac condition. Among the patients who were not studied, no obvious differences were observed, except for a slightly higher ICP. Finally, the time at which the brain tissue PO₂ recordings were made, relative to the time after SAH, was similar in both of the groups that were studied.

Discussion

In this prospective observational study we continuously monitored brain tissue PO₂ in 11 patients with poor-grade aneurysmal SAH whose blood pressure was stable dur-
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Fig. 2. Bar graph showing MABP (mean ± SD) following the administration of 60 mg of nimodipine (26 separate observations) in seven patients with a poor clinical grade post-SAH.

Fig. 3. Bar graph showing CPP (mean ± SD) following the administration of 60 mg of nimodipine (26 separate observations) in seven patients with poor-grade SAH.

Nimodipine for Vasospasm

Cerebral vasospasm is a well-known cause of incidences of major morbidity and mortality after aneurysmal SAH.8,9 In the International Cooperative Study on the Timing of Aneurysm Surgery,24,25 for example, DINDs were responsible for disability in 7.2% of patients and death in 6.3%. A variety of treatments have been proposed to manage vasospasm or to limit its effects.9,31 Among these various treatments, nimodipine, a calcium antagonist, is recommended for routine use in the guidelines for treating ruptured cerebral aneurysms published by the American Heart Association.32

The rationale for using calcium antagonists such as nimodipine to manage vasospasm was established because of their vasodilatory effects on cerebral arteries.11,19,37 The clinical use of nimodipine has been supported by several randomized clinical trials,1,34,38,39,41 a metaanalysis of these investigations,3 and a systematic review of clinical trials of calcium antagonists in patients with SAH. These various reports have demonstrated an association between nimodipine use and improved outcome among patients with all grades of SAH. In addition, nimodipine has been shown to reduce the incidence of poor outcome due to delayed cerebral ischemia associated with vasospasm;12 this decrease resulted from a reduction in the occurrence of DINDs.12 These various trials, however, failed to demonstrate that nimodipine had any effect on the diameters of cerebral vessels. Conversely, in clinical studies the calcium-channel antagonist nicardipine has been shown to reduce the incidence of both symptomatic vasospasm and vasospasm identified on angiograms. Moreover, in randomized studies nicardipine use was associated with improved patient outcome.16-18 It is not precisely defined how nimodipine use improves outcome after SAH, and this uncertainty prompted us to investigate the effects of nimodipine on brain tissue PO2.

Physiological Effects of Nimodipine

There is clinical evidence that calcium-channel blocking agents reduce the occurrence of delayed ischemic deficits and thereby improve the clinical outcome of patients with SAH. Nevertheless, neither of the two mechanisms of ac-
tion postulated—maintenance of CBF and neuronal protection—has been conclusively shown to explain these beneficial effects.12 Furthermore, nimodipine has been found to be ineffective in stroke treatment4 and its use in clinical trials of stroke has been criticized in retrospect because only 50% of published animal studies support its value as a neuroprotective agent.13 The findings in this report may, in part, explain this disparity in nimodipine’s efficacy as a neuroprotectant.

There are no clinical studies to date in which the acute cerebral biochemical effects of nimodipine following aneurysmal SAH have been investigated. With the application of multimodality monitoring we have been able to examine the effects of interventions aimed at ameliorating cerebral vasospasm. We report that, although nimodipine has been shown to improve outcome following SAH, it temporarily reduces brain tissue PO2, in two thirds of patients who have stable blood pressure. The exact cause of this transient reduction in PO2 is presently unknown. In this study the only significant difference between patients with stable pressures and those with transient reductions in PO2 was patient weight: patients in whom transient reductions in brain tissue PO2 occurred were on average lighter. In addition, more patients with reductions in brain tissue PO2 had a history of cardiac disease. These variables may alter the pharmacokinetics and drug levels of nimodipine because its prescribed dosage is not based on patient weight. There is anecdotal information indicating that many physicians reduce the nimodipine dosage in patients in whom MABP decreases. Our results indicate that more careful dosing may also need to be based on weight. A second explanation may be that there is a transient CBF reduction; this has been observed in previous animal models.10 Further studies of CBF and cerebral autoregulation as well as biochemical analyses performed using microdialysis will be needed to elucidate the biochemical and neurochemical pathways associated with nimodipine administration for vasospasm. In the patients described in this report decreased CPP due to nimodipine-associated reductions in MABP did not appear to be a contributing factor because those patients whose blood pressure did not remain stable were excluded from this analysis.

There is only one case report in which hypoxia has been shown to result from nimodipine administration.6 In that case systemic hypoxia occurred following nimodipine administration in a patient with traumatic SAH and acute respiratory distress syndrome and in whom brain tissue PO2 was not monitored. The authors speculated that the hypoxemia was due to vasodilation, which shunted blood away from areas of adequate lung ventilation, increasing the ventilation/perfusion mismatch. Although this mechanism cannot be excluded, it is unlikely that it occurred in our patients because in all cases chest x-ray films obtained at the time of study revealed relatively normal findings. Furthermore, during the study systemic SaO2 levels were measured in each patient, but no reduction in SaO2 was found. Whether there was cerebral shunting of blood due to vasodilation remains to be determined.

Conclusions

Following SAH, patients are vulnerable to clinically identifiable secondary injuries, including vasospasm, that may be responsible for neurological deterioration. Approximately one third of all patients with cerebral vasospasm experience DINDs, which may resolve or progress to permanent cerebral infarction. There is presently limited direct feedback regarding how the brain responds to treatments for vasospasm, in general, and to calcium-channel blocking agents, in particular. Implementation of a multimodality monitoring system such as brain tissue PO2 monitoring can help elucidate the biochemical cascades associated with SAH and vasospasm. Our results indicate that carefully documented bio- and neurochemical effects of various vasospasm treatments may aid us in the establishment of a paradigm against which future therapies and interventions may be tested.

References

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